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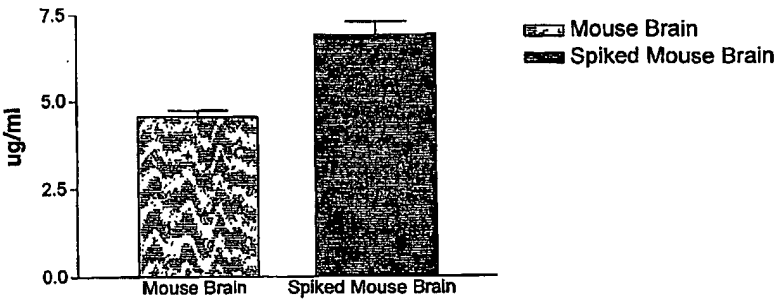
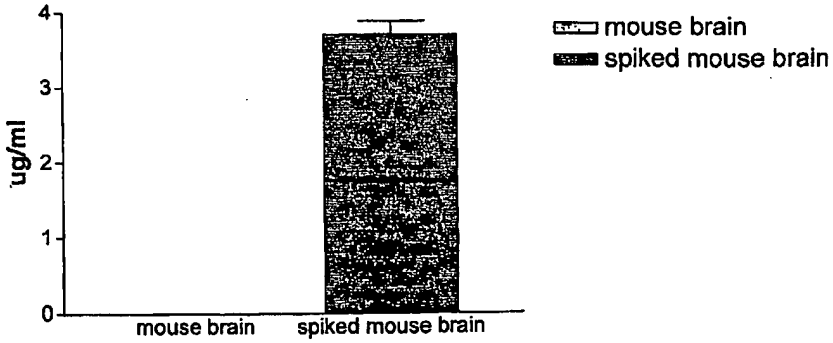
[Continued on next page]

(54) Title: ANTIBODIES TO ALPHA-SYNUCLEIN



A



B

(57) Abstract: The invention provides methods for detecting alpha-synuclein. The invention also identifies preferred epitopes of alpha synuclein for use in such detection, and provides antibodies specifically binding to such epitopes.

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SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/37444

A. CLASSIFICATION OF SUBJECT MATTER
IPC: C07K 16/18(2006.01);C12P 21/08(2006.01);G01N 33/53(2006.01)

USPC: 530/388.1,387.3;435/70.21,7.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 530/388.1, 387.3; 435/70.21, 7.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	JAKES, R. et al. Epitope Mapping of LB509, a Monoclonal Antibody Directed Against Human alpha-Synuclein. Neuroscie Lett. July 1999, Vol. 269, pages 13-16, especially page 13 and 14.	1-3, 16, 26, 32-34, 45 --- 46
Y	US 2002/0094335 A1 (CHALIFOUR et al.) 18 July 2002 (18.07.2002), paragraphs [0069, 0099, 0126].	46
A	GIASSON, B.I. et al. A Panel of Epitope-Specific Antibodies Detects Protein Domains Distributed Throughout Human alpha-Synuclein in Lewy Bodies of Parkinson's Disease. J. Neurosci Res. February 2000, Vol. 59, pages 528-533, especially page 530.	18-19
A	LIPPA, C.F. et al. Alpha-Synuclein in Familial Alzheimer Disease. Archives Neurol. November 2001, Vol. 58, pages 1817-1820.	4-5, 27-29

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
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INTERNATIONAL SEARCH REPORT

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Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: Please See Continuation Sheet

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

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BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 5 and each of claims 1-4, 16, 18, 19, 26-29, 32-34 and 45-46 in part, drawn to a monoclonal antibody that competes with an antibody that specifically binds to residues 109-120 of alpha synuclein.

Group II, claim(s) 6, 7, 24, 25 and each of claims 1-4, 16, 18, 19, 29, 32-34 and 45-46 in part, drawn to a monoclonal antibody that competes with an antibody that specifically binds to an epitope on the C-terminus of synuclein.

Group III, claim(s) 8, 22, 23, and each of claims 1-4, 16, 18-19, 29. 32-37and 45-46 in part, drawn to a monoclonal antibody that competes with an antibody that specifically binds to an epitope on the N-terminus of synuclein.

Group IV, claim(s) 9, 10, and each of claims 1-4, 16, 18-19, 28-29, 32-34 and 45-46 in part, drawn to a monoclonal antibody that competes with an antibody that specifically binds to an epitope comprising residues 43-51 and 56-65 of synuclein.

Group V, claim(s) 11, 17, and each of claims 1-4, 16, 18, 19, 28-29, 32-34 and 45-46 in part, drawn to a monoclonal antibody that competes with an antibody that specifically binds to an epitope comprising residues 118-126 of alpha synuclein.

Group VI, claim(s) 12 and each of claims 1-4, 16, 18, 19, 26-29, 32-37 and 45-46 in part, drawn to a monoclonal antibody that competes with an antibody that specifically binds to an epitope comprising residues 91-99 of synuclein.

Group VII, claim(s) 13 and each of claims 1-4, 16, 18-19, 29, 32-37 and 45-46 in part, drawn to a monoclonal antibody that competes with an antibody that specifically binds to an epitope comprising residues 40-55 of synuclein.

Group VIII, claim(s) 14, 20, 21, 30 and each of 1-4, 16, 18-19, 26-27, 29, 32-34 and 45-46 in part, drawn to a monoclonal antibody that competes with an antibody that specifically binds to an epitope comprising residues 124-134 of alpha synuclein, wherein residue 129 is phosphorylated serine.

Group IX, claim(s) 15, 31 and each of claims 1-4, 16, 18-19, 29, 32-34 and 45-46 in part, drawn to a monoclonal antibody that competes with an antibody that specifically binds to an epitope comprising residues 123-127 of alpha synuclein, wherein residue 125 is nitrated tyrosine.

Group X, claim(s) 38-44, drawn to a pair of monoclonal antibodies, each specifically binding to a different epitope within synuclein.

Group XI, claim(s) 47-48, drawn to a method of humanizing a monoclonal antibody of Table 1 or of producing a chimeric form of an antibody of Table 1.

Group XII, claim(s) 49-70 and 75-76, drawn to a method for detecting alpha synuclein in a fluid sample, comprising the use of a capture antibody and a reporter antibody.

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Group XIII, claim(s) 71-73, drawn to a method of monitoring processing of alpha-synuclein to a fragment comprising the use of a cultured cells expressing alpha synuclein.

Group XIV, claim(s) 74, drawn to a method of screening an agent for activity in inhibiting processing or secretion of alpha synuclein.

The inventions listed as Groups I-XIV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The technical feature linking groups I-XIV appears to be a monoclonal antibody as shown in Table 1 that specifically binds to alpha synuclein. As such, the first recited special technical feature of the first claim and the first antibody of Table 1 would be: A monoclonal antibody that competes with monoclonal antibody 7G4 (JH4) for specific binding to alpha synuclein, wherein the epitope for 7G4 is residues 109-120 of alpha synuclein.

However, Jakes et al. (*Neurosci. Lett.* July 1999; 269: 13-16) teaches the monoclonal antibody LB509, which is directed against human alpha-synuclein and recognizes amino acids 115-122 of alpha-synuclein (see abstract). Jakes et al. demonstrate that peptides consisting of residues 110-122 of alpha synuclein were capable of interfering with antibody binding (see Figure 2, p. 15). The monoclonal antibody taught by Jakes et al. would therefore be expected to compete with the instantly claimed monoclonal 7G4 for specific binding to alpha synuclein. Accordingly, the technical feature linking the inventions of Groups I-XIV does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.

The special technical feature of Group I is considered to be a monoclonal antibody that binds to an epitope comprising residues 109-120 of alpha-synuclein, which is not required by groups II-XIV.

The special technical feature of Group II is considered to be a monoclonal antibody that binds to an epitope comprising the C-terminus of alpha-synuclein, which is not required by groups I or III-XIV.

The special technical feature of Group III is considered to be a monoclonal antibody that binds to an epitope comprising the N-terminus of alpha-synuclein, which is not required by groups I-II or IV-XIV.

The special technical feature of Group IV is considered to be a monoclonal antibody that binds to an epitope comprising residues 43-51 and 58-65 of alpha-synuclein, which is not required by groups I-III or V-XIV.

The special technical feature of Group V is considered to be a monoclonal antibody that binds to an epitope comprising residues 118-126 of alpha-synuclein, which is not required by groups I-IV or VI-XIV.

The special technical feature of Group VI is considered to be a monoclonal antibody that binds to an epitope comprising residues 91-99 of alpha-synuclein, which is not required by groups I-V or VII-XIV.

The special technical feature of Group VII is considered to be a monoclonal antibody that binds to an epitope comprising residues 40-55 of alpha-synuclein, which is not required by groups I-VI or VIII-XIV.

The special technical feature of Group VIII is considered to be a monoclonal antibody that binds to an epitope comprising residues 124-134 of alpha-synuclein, wherein residue 129 is phosphorylated serine, and which is not required by groups I-VII or IX-XIV.

The special technical feature of Group IX is considered to be a monoclonal antibody that binds to an epitope comprising residues 123-127 of alpha-synuclein, wherein residue 125 is nitrated serine, and which is not required by groups I-VIII or X-XIV.

The special technical feature of Group X is considered to be a pair of monoclonal antibodies, each specifically binding to a different epitope within synuclein, which is not required by groups I-IX or XI-XIV.

The special technical feature of Group XI is considered to be a method of humanizing a monoclonal antibody of Table 1 or of producing a chimeric form of an antibody of Table 1, which is not required by groups I-X or XII-XIV.

The special technical feature of Group XII is considered to be a method for detecting alpha synuclein in a fluid sample, comprising the use of a capture antibody and a reporter antibody, which is not required by groups I-XI or XIII-XIV.

The special technical feature of Group XIII is considered to be a method of monitoring processing of alpha-synuclein to a fragment comprising the use of a cultured cells expressing alpha synuclein, which is not required by groups I-XII or XIV.

The special technical feature of Group XIII is considered to be a method of screening an agent for activity in inhibiting processing or secretion of alpha synuclein, which is not required by groups I-XIII.

Accordingly, Groups I-XIV are not so linked by the same or corresponding special technical feature as to form a single general inventive concept.

Continuation of Box III Item 4:
5 in full, and each of 1-4, 16, 18-19, 26-29, 32-34 and 45-46 in part, to the extent of a monoclonal antibody recognizing an epitope comprising residues 109-120 of alpha synuclein

Continuation of B. FIELDS SEARCHED Item 3:
EAST (PGPUB, USPAT, EPO, DERWENT)
STN (MEDLINE, BIOSIS, EMBASE, SCISEARCH, CAPLUS)
search terms: synuclein, antibody, monoclonal, 109-120, C or carbox? terminal, 7G4, 6A8, 5C12, 6A12